

REMARKS

At the outset, Applicants wish to thank Examiner Zucker for indicating that Claim 10, as previously presented, was free of the prior art. Applicants submit that, in view of the present amendments and remarks, all of the pending claims are allowable.

Present Claims 5-9, 11 and 16 relate to methods for preparing A-type crystals of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester, comprising:

crystallizing N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester from a solution comprising N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester and a solvent, to obtain A-type crystals of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester,

wherein said solvent is selected from the group consisting of water and mixtures of water and a lower alcohol,

wherein said crystallizing is carried out such that the temperature of said solution is maintained above 30°C until onset of nucleation of said A-type N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester.

Present Claims 12-15, 17, and 18 relate to methods for preparing A-type crystals of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester, comprising:

crystallizing N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester from a solution comprising N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester and a solvent, to obtain A-type crystals of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester,

wherein said solvent is selected from the group consisting of water and mixtures of water and a lower alcohol,

wherein said crystallizing is carried out in the presence of seed crystals of A-type N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester.

The inventors have surprisingly found that the presently claimed methods yield an especially stable form of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester (hereinafter referred to as “neotame”), which is referred to as the A-type crystal form. At the outset, it must be emphasized that the present inventors *were the first to find* that A-type crystal exhibits excellent stability (see, *e.g.*, page 4, Table 1 and the surrounding description thereof, of the instant specification) as compared to the other polymorphic forms of neotame such as the B-type, G-type, and the like. The excellent stability of the A-type crystals is, in turn, very useful from the commercial point of view (see, *e.g.*, paragraph bridging pages 1 and 2, of the instant specification).

The cited references contain no disclosure or suggestion of the presently claimed methods or the advantages afforded thereby. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 5-9 and 11 under 35 U.S.C. §102(b) or, in the alternative, under 35 U.S.C. §103(a) in view of U.S. Patent No. 5,510,508 (Claude et al); and the rejection of Claims 12-15 under 35 U.S.C. §103(a) in view of Claude et al in view of WO 93/021101 (Tosoh et al) are respectfully traversed.

As shown in Examples 1-5, Claude et al discloses the preparation of neotame by a process in which aspartame is reductively reacted with 3,3-dimethylbutyraldehyde in the presence of a platinum or palladium catalyst in a solvent which is a mixture of a 0.1 M aqueous solution of acetic acid and methanol. After the reaction is complete, the catalyst is removed by filtration, and the pH of the filtrate is adjusted to 5 by the addition of a few drops

of a 1 N solution of sodium hydroxide. The methanol is “then removed under vacuum, the temperature being kept below 40°C,” and a “white solid rapidly precipitates.”

Thus, the precipitation described in Claude et al does not involve carrying out the crystallization “such that the temperature of said solution is maintained above 30°C until onset of nucleation of said N-[N-(3,3-dimethylbutyl)-L- -aspartyl]-L-phenylalanine methyl ester.” Instead, Claude et al merely discloses that the “temperature being kept below 40°C.” Thus, Claude et al only states an upper temperature limit which was not exceeded and says nothing about any lower temperature limit. In fact, Claude et al never states any actual temperature, only that it is below 40°C. Just how much below 40°C is unstated.

Perhaps even more importantly, Claude et al does not even disclose what temperature is “kept below 40°C.” In this regard, it is evident that Examples 1-5 of Claude et al were carried out on a bench-top scale. Temperature control during the removal of methanol by evaporation under vacuum in such situations is typically achieved by placing the vessel in a water bath and monitoring-controlling the temperature of the water bath. Thus, one of skill in the art would understand that the Examples of Claude et al were carried out by maintaining the temperature of a water bath, not the filtrate itself, below 40°C. In fact, on page 7 of the Official Action dated September 26, 2002, it is stated that the “Examiner agrees with Applicants that this would be a natural assumption....”

Furthermore, as explained in detail previously, the method of Claude et al does not yield A-type crystals. For all of these reasons, the methods of the present claims are quite distinct from that of Claude et al. Accordingly, this reference cannot anticipate the present claims.

As for Claims 12-15, Applicants note that these claims recite the use of a specific type of seed crystals (A-type seed crystals). In sharp contrast, Claude et al not only is silent in

regard to the use of any type of seed crystals, but also contains no disclosure of A-type crystals or method for preparing A-type crystals.

In support of these assertions, applicants again cite the experiments carried out by Mr. Kawahara as described previously and reported in the duly executed declaration under 37 C.F.R. § 1.132 (“the first Kawahara Declaration”). As reported in the first Kawahara Declaration, Mr. Kawahara has carried out a substantial repetition of Example 1 of Claude et al and found that the method resulted in too low a yield of neotame, *i.e.*, a 50-60% yield. Mr. Kawahara then carried out another substantial repetition of Examples 1 and 2 of Claude et al and found that the “white solid” rapidly precipitated in Examples 1 and 2 of Claude et al are also B-type crystals.

On the other hand, Example 1 of Claude et al indeed discloses that “The methanol is then removed by evaporation under vacuum, the temperature being kept below 40°C. A white solid rapidly precipitates.” However, as explained above, it is obvious to those who are skilled in the art that the temperature which kept below 40°C is that of the water in the water bath, and not that of the content or mass in the vessel.

In fact, during his substantial repetitions of Examples 1 and 2 of Claude et al, Mr. Kawahara checked the temperature of the mass in the vessel often and found that the temperature of the mass inside the vessel was, in fact, about 23-28°C, which is below the nucleation temperature of 30°C or greater recited in the present claims. The temperature drop or difference between the bath (40°C) and the mass inside the vessel (about 23°C) is reasonably attributed to the heat of vaporization of the methanol.

Moreover, it is understood from the results of Experiment II as described at the first full paragraph on page 10 of the of the second Kawahara Declaration, that neotame is difficult to crystallize at a temperature of above 30°C, because it was formed in the form of a

viscous oil at that temperature. Substances formed as oils usually need a longer time to crystallize. To the contrary, rapid crystallization was observed in Claude et al, and it is thought that the driving force for such rapid crystallization was presumably due to the cooling effect which was, in turn, caused by evaporation by the methanol under reduced pressure, whereby the inside liquid temperature was naturally decreased to below 30°C, and the crystallization naturally occurred at below 30°C. Moreover, it is reasonable that neotame, which is apt to form an oil, requires a long time to nucleate, if it is to be crystallized at, *e.g.*, 35°C, and cannot be crystallized rapidly.

For all of these reasons, the present claims are fully patentable over the teachings of Claude et al.

Tosoh indeed discloses the so-called seeding crystallization of Aspartame. However, Tosoh is completely silent in regard to the crystallization of neotame, the use A-type crystals of neotame as seed crystals, or even the existence of A-type crystals of neotame.

On page 9 of the Official Action dated September 26, 2002, it is asserted that “neotame and aspartame would be expected to be very similar.” It is also asserted that it would have been obvious to apply the seeding method of Tosoh to the crystallization of neotame. However, this logic is incorrect for the following reasons.

First, Applicants agree that Aspartame is somewhat related in structure to neotame. However, neotame is structurally similar to Aspartame only in the sense that neotame contains one Aspartame residue in addition to one 3,3-dimethylbutyl moiety. Therefore, if a chemical reaction involves some reaction site on an Aspartame molecule, neotame might behave like Aspartame in such a reaction. Thus, it might be said that neotame is related in certain chemical properties to Aspartame, only in this sense. Of course, in many chemical properties neotame and Aspartame react quite differently. For example, any reaction which relies on the presence of a NH<sub>2</sub> group will not be possible with neotame.

Applicants also concede that Aspartame and neotame share, to a certain degree, the physiological property of imparting a sweet taste. However, the magnitude of this property is much greater for neotame.

In any event, Applicants submit that the process of crystallization is not related to the chemical reactivity of certain functional groups present in either Aspartame itself or the aspartame residue contained in neotame. Applicants further submit that crystallization is not a physiological property.

Instead, crystallization is a physical phenomenon, and at most a physico-chemical phenomenon. It is obvious and well known that the physical properties of neotame are quite distinct from those of Aspartame. For example the molecular weight of neotame is about 378 daltons, while that of Aspartame is only about 294 daltons. Moreover, neotame will have a vastly different shape as compared to Aspartame owing to the presence of the additional and relatively voluminous 3,3-dimethylbutyl group.

When viewed from the perspective of physico-chemical properties, it is seen that the seeding crystallization of Aspartame does not suggest the presently claimed seeding crystallization of neotame, because Neotame and Aspartame are quite different from each other in physical structure and therefore, in *physical properties*.

In fact, the different natures of Aspartame and neotame are supported by the disclosure of Tosoh itself. Thus, according to Tosoh, the seeding crystallization of Aspartame is for the purpose of obtaining Aspartame crystals *having a larger width to length ratio*, no polymorphism being involved therein (see Abstract on the front page of Tosoh). In sharp contrast, the presently claimed seeding crystallization is for the purpose of obtaining the same type, *i.e.*, A- type crystals of neotame as the seed crystals type.

If the assertions in the Official Action were correct, one would naturally expect that the presently claimed seeding crystallization would afford neotame crystals having a larger width to length ratio. This is, however, definitely not the case.

In any event, even if one were to combine the teachings of Tosoh with those of Claude et al, one would still not arrive at the presently claimed seeding method. As noted above, Claude et al contains no disclosure of A-type crystals of neotame or a method of making A-type crystals of neotame. Certainly, there is no disclosure of A-type crystals of neotame in Tosoh. Thus, even if the teaching of these two references were combined, at most one would arrive at a process in which B-type crystals of neotame were used as the seed crystals.

In sharp contrast, present Claims 12-15, 17, and 18 explicitly recite the use of A-type seed crystals.

On pages 7 and 8 of the Official Action dated August 26, 2003, the position is taken that Experiment I in the second Kawahara Declaration is not a true side-by-side comparison, because:

[i]t assumes that Claude's teaching that a temperature of below 40°C is maintained during evaporation/crystallization means that the *bath* temperature is maintained at the required temperature and not the crystallization solution itself. The Examiner contends that Claude teaches control of the temperature of the solution itself.

However, this assertion is belied by the statement by the same Examiner on page 7 of the Office Action dated September 26, 2002:

Applicant further argues that the temperature employed by Claude corresponds to a bath temperature and not the internal temperature of the crystallization solution. The *Examiner agrees with Applicants that this would be a natural assumption* but points out that it is not supported by the facts of the record.

Applicants submit that there is nothing in the record to support the assertion that the temperature mentioned in Claude et al relates to the internal crystallization solution rather than the bath. Applicants also agree with the Examiner that it is natural to assume that the temperature referred to in Claude et al is the bath temperature, not the solution temperature.

For these reasons, the criticism of Experiment I of the second Kawahara Declaration is misplaced and should be withdrawn.

Accordingly, the rejections should be withdrawn.

In addition, the Examiner's attention is directed toward new Claims 19-29, which all recite that the "crystallizing is carried out such that the temperature of said solution is maintained at 40°C to 50°C until onset of nucleation of said A-type N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester." In other words, Claims 19-29 all include the limitation of Claim 10, as previously presented. Applicants submit that Claims 19-29 are patentable over the cited references for the same reasons that Claim 10 was not rejected in view of these references. Thus, Claims 19-29 should certainly be allowed.

The rejection of claims 5-15 under 35 U.S.C. §112, second paragraph, has been, in part, obviated by appropriate amendment and is, in part, respectfully traversed. As noted above, Claims 5 and 12 have been amended to replace the term "crystals of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester which exhibit at least the following diffraction peaks as measured by x-ray diffraction, 2 $\theta$  CuK $\alpha$ : a peak at 6.0°; a peak at 24.8°; a peak at 8.2°; and a peak at 16.5°" with "A-type crystals of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester." Thus, amended Claims 5 and 12 are free of the criticisms outlined on pages 2-3 of the Office Action dated August 26, 2003.



Specifically, applicants note that the term “A-type” crystals in the context of N-[N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl]-L-phenylalanine methyl ester is a term of art recognized by those of skill in the art. In support of this position, Applicants direct the Examiner’s attention to Claims 8 and 9 of U.S. Patent No. 6,372,278 (Ishida et al, copy attached hereto as Exhibit A).

As for Claims 16-18, 23, 28, and 29, Applicants submit that the use of characteristic peak values is accepted by those of skill in the art for identifying a specific crystalline form of a particular compound. In fact, this Examiner has approved the recitation of selected characteristic peak values for identifying a specific crystalline form, even though the compound exhibits addition peaks. In support of this assertion, Applicants cite U.S. Patent No. 6,673,838 (Hadfield et al, copy attached hereto as Exhibit B). As the Examiner will note, Claim 5 of Hadfield et al recites only a handful of the peaks shown in Figure 1. Thus, even this Examiner has approved the recitation of selected peaks from an x-ray diffraction pattern to define a crystal form.

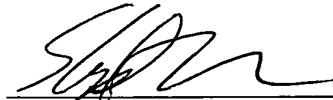
Accordingly, the rejection is improper and should be withdrawn.

Application No. 09/830,159  
Preliminary Amendment

Applicants submit that the present application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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